Disputes & Debates: Editors' Choice

Editors' Note: Teaching NeuroImage: Atypical Unilateral Cortical Ribboning in Anti-NMDA Receptor Encephalitis

Dr. Chen et al. reported the case of a 62-year-old man presenting with confusion, agitation, and pressured tangential speech after a car accident, whose brain MRI showed left-hemispheric cortical ribboning. EEG showed left-hemispheric slowing but no epileptiform activity. The patient's cerebrospinal fluid (CSF) was positive for anti-NMDA receptor antibodies. The authors diagnosed this as an atypical presentation of anti-NMDA receptor encephalitis. In response, Dr. Budhram and colleagues inquire whether testing was performed for antibodies against myelin oligodendrocyte glycoprotein (anti-MOG), noting that unilateral cortical abnormalities are seen in patients with anti-MOG–associated encephalitis with seizures (FLAMES), a minority of whom also harbor coexistent anti-NMDA receptor antibodies. They also inquire about the availability of susceptibility-weighted imaging (SWI) sequences, to look for underlying calcification or contusion, and whether the neuroimaging abnormalities resolved after immunotherapy. The readers also seek further clarification about the presence of other typical features of anti-NMDA receptor encephalitis and details about the antibody test methodology to allay concerns about false positivity. In another reader response, Dr. Scheel and colleagues note that most of the patients with anti-NMDA receptor encephalitis have normal MRI findings or just subtle white matter lesions, in contrast to the high frequency of cortical ribboning in patients with Creutzfeldt-Jakob disease (CJD), a subset of whom can have anti-NMDA receptor antibodies in their serum (i.e., the diagnosis of anti-NMDA receptor encephalitis should be confirmed by CSF testing, but even rare false-positive studies have been noted here as well). Therefore, they inquire whether CJD workup was performed in the patient and seek similar clarification about the details of antibody testing and about any subsequent immunotherapy given the patient's reported incomplete recovery. Unfortunately, despite our efforts to contact the authors, we received no response regarding these important reader comments. This exchange highlights important considerations regarding the differential diagnosis of cortical ribboning in the setting of subacute changes in mental status.

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Neurology® 2023;100:886. doi:10.1212/WNL.0000000000207330

Reader Response: Teaching NeuroImage: Atypical Unilateral Cortical Ribboning in Anti-NMDA Receptor Encephalitis

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Neurology® 2023;100:886–887. doi:10.1212/WNL.0000000000207331

We read with interest this case by Chen et al.[1] regarding a reportedly atypical presentation of anti-NMDA receptor (NMDAR) encephalitis with unilateral cortical ribboning. Although unusual for anti-NMDAR encephalitis, unilateral cortical abnormalities are observed in patients with unilateral cortical fluid-attenuated inversion recovery (FLAIR)-hyperintense lesions in anti-myelin oligodendrocyte glycoprotein (MOG)–associated encephalitis with seizures (FLAMES),

Author disclosures are available upon request (journal@neurology.org).

a minority of whom harbor co-existent anti-NMDAR.[2] Was anti-MOG testing performed, and if so, by what methodology?

Additionally, on axial T2-FLAIR sequences, there is a "mottled" appearance to the abnormal cortex, potentially in keeping with calcification or contusion that could cause seizure (with associated seizure-related change on diffusion-weighted imaging). Was susceptibility-weighted imaging also available for review, and did all neuroimaging abnormalities resolve after immunotherapy?

Finally, further information regarding whether more typical features of anti-NMDAR encephalitis were present (e.g., prodromal symptoms preceding car accident, CSF inflammation) and details surrounding anti-NMDAR test methodology (e.g., whether positivity was demonstrated by 2 assays) would help inform the likelihood of anti-NMDAR false positivity, which has rarely been reported even when testing CSF.[3]

Clarifying the above points in this case ensures there is no concern for "phenotype creep," whereby the features of alternative diagnoses such as unilateral cortical FLAMES or seizure-related changes are mistakenly assumed to broaden the clinical spectrum of a neural antibody such as anti-NMDAR.[4]

1. Chen AY, Wang DS, Sawlani K. Teaching NeuroImage: Atypical unilateral cortical ribboning in anti-NMDA receptor encephalitis. *Neurology*. 2022;99(23). doi:10.1212/WNL.0000000000201368
2. Budhram A, Mirian A, Le C, Hosseini-Moghaddam SM, Sharma M, Nicolle MW. Unilateral cortical FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures (FLAMES): characterization of a distinct clinico-radiographic syndrome. *J Neurol*. 2019;266(10):2481-2487. doi:10.1007/s00415-019-09440-8
3. Ardakani RV, Vernino S, Blackburn K. False positive cerebrospinal fluid NMDA receptor antibodies: a single center case series. Poster Presented at: American Academy of Neurology Summer Conference. San Francisco; July 15, 2022. Abstract 039.
4. Budhram A, Mills JR, Shouman K, Dyck PJB, Hassan A, Zalewski NL. False-positive anti-neuronal nuclear antibody type 1 in a patient with RFC1 repeat expansion: preventing "phenotype creep" in autoimmune neurology. *J Neurol Sci*. 2020;416:117018. doi:10.1016/j.jns.2020.117018

Reader Response: Teaching NeuroImage: Atypical Unilateral Cortical Ribboning in Anti-NMDA Receptor Encephalitis

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Neurology® 2023;100:887. doi:10.1212/WNL.0000000000207332

We read with great interest the report by Chen et al.[1] on unilateral cortical ribboning in a 62-year-old man with NMDA receptor (NMDAR) antibodies. Most patients with NMDAR encephalitis (50%–75%) have no MRI abnormalities or only subtle white matter lesions.[2] By contrast, cortical ribboning is frequently observed in patients with Creutzfeldt-Jakob disease (CJD) and also in those with asymmetric or strictly unilateral presentation.[3] Furthermore, NMDAR antibodies have been reported in the serum of patients with CJD,[4] although not in CSF.[5]

We would inquire whether CJD workup (e.g., RT-QuIC, 14-3-3) was performed in the reported patient. It would also be interesting to report the CSF antibody titer, how antibody testing was performed (i.e., cell-based assay, confirmed with indirect immunofluorescence on brain sections), and whether a second-line immunotherapy was considered given the incomplete recovery of the patient. As short-term clinical follow-up usually confirms or excludes CJD, information on the disease course would also be valuable. Otherwise, case reports with highly atypical presentation of very rare diseases bear the risk of future neurologists thinking of zebras—not horses—when they hear the hoofbeat.

1. Chen AY, Wang DS, Sawlani K. Teaching NeuroImage: Atypical unilateral cortical ribboning in anti-NMDA receptor encephalitis. *Neurology*. 2022;99(23):1062-1063. doi:10.1212/WNL.0000000000201368
2. Heine J, Prüss H, Bartsch T, Ploner CJ, Paul F, Finke C. Imaging of autoimmune encephalitis—relevance for clinical practice and hippocampal function. *Neuroscience*. 2015;309:68-83. doi:10.1016/j.neuroscience.2015.05.037.
3. Yung B, Moeller JJ, Bitar M, Chong D. Teaching NeuroImages: hemispheric-onset Creutzfeldt-Jakob disease with concordant MRI and EEG findings. *Neurology*. 2010;75(16):e66. doi:10.1212/WNL.0b013e3181f881be
4. Mackay G, Ahmad K, Stone J, et al. NMDA receptor autoantibodies in sporadic Creutzfeldt-Jakob disease. *J Neurol*. 2012;259(9):1979-1981.
5. Grau-Rivera O, Sánchez-Valle R, Saiz A, et al. Determination of neuronal antibodies in suspected and definite Creutzfeldt-Jakob disease. *JAMA Neurol*. 2014;71(1):74-78.

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Neurology 2023;100;887
DOI 10.1212/WNL.0000000000207332